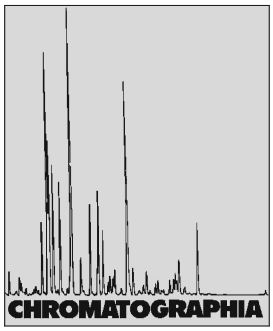
Enantiomeric Resolution of a Chiral Sulfoxide Series by LC on Synthetic Polymeric Columns with Multimodal Elution



2010, *71*, 361–372

Tiago C. Lourenço[1], Daniel W. Armstrong[2], Quezia Bezerra Cass[1,✉]

[1] Chemistry Department, Federal University of São Carlos, P.O. Box 676, São Carlos, SP 13.565-970, Brazil; E-Mail: quezia@pq.cnpq.br
[2] Chemistry and Biochemistry Department, The University of Texas at Arlington, Arlington, TX, USA

Received: 8 October 2009 / Revised: 5 December 2009 / Accepted: 16 December 2009
Online publication: 21 January 2010

Abstract

The liquid chromatography enantiomeric separation of a series of 17 chiral sulfoxides was systematically investigated using multimodal elution with the new synthetic polymeric stationary phases P-CAP, P-CAP DP and DEAVB. The sulfoxide series was composed of aryl alkyl sulfoxides, benzoimidazole sulfoxides and the drugs modafinil, albendazole sulfoxide, omeprazole, lansoprazole, pantoprazole and rabeprazole. This work examines the effectiveness of the polymeric chiral stationary phases for the separation of chiral sulfoxides and describes the superiority of DEABV for these separations in three different elution modes. The first ever reversed phase enantiomeric separations on these columns is demonstrated.

Keywords

Column liquid chromatography
Enantiomeric separations
Synthetic polymeric column
Chiral sulfoxides

Introduction

Organic sulfoxides have a pyramidal space configuration with an isolated pair of electrons occupying the pseudo-tetrahedron center [1]. Due to their high energetic barrier, approximately 40 Kcal mol^{-1} [2], their conformation is usually stable below 200 °C [3], allowing them to be separated and isolated as enantiomers.

The first resolution of chiral sulfoxides was reported in 1926 [4]. Since then, they have been studied extensively given their importance in asymmetric synthesis and in various industries [3–5].

A variety of different types of chiral stationary phases (CSPs) has been effective for the separations of chiral sulfoxides. Cyclodextrin-based CSPs provided effective and efficient resolution for a variety of sulfoxides using gas chromatography [6] and high-pressure liquid chromatography [5]. Protein-based CSPs [7] and the macrocyclic glycopeptides CSPs [8] were effective for the enantioresolution of a range of chiral sulfoxides. Polysaccharide-based CSPs are the most useful in successfully resolving many chiral sulfoxides [9–12]. Therefore, these CSPs are frequently used for quantification of chiral drugs that have the sulfur atom as the stereogenic center [13, 14].

Recently, new polymeric chiral stationary phases based on the monomers: *N*-(2-acryloylamino-(1*R*,2*R*)-cyclohexyl)-acrylamine (P-CAP) [15–17], *N*,*N*′-[(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediyl]bis-2-propenamide (P-CAP DP) [18] and trans-9,10-dihydro-9,10-ethanoanthracene-(11*S*,12*S*)-11,12-dicarboxylic acid bis-4-vinylphenylamide (DEAVB) [19] have been developed (Fig. 1).

These polymeric CSPs produced efficient separations of a diverse number of chiral compounds when used in the normal and polar organic elution mode [15, 18, 19]. We, therefore, evaluated

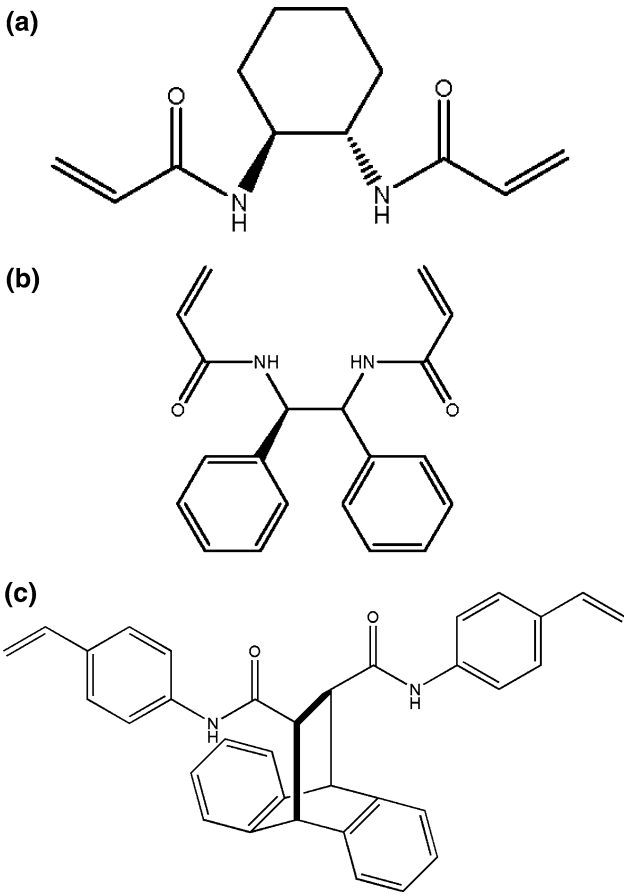


Fig. 1. Chemical structures of the monomers of (**a**) P-CAP, (**b**) P-CAP DP and (**c**) DEAVB

these CSPs for the enantiomeric resolution of a series of chiral sulfoxides (Fig. 2) composed of aryl alkyl sulfoxides, benzoimidazoles sulfoxides and some sulfoxide drugs. This work expands the systematic work on separation of chiral sulphoxides [9, 11, 20, 21] and reports the results obtained of these new polymeric CSP.

Experimental

Materials

Methanol, 2-propanol, acetonitrile were LC grade and obtained from J.T. Baker (Phillipsburg, USA), dichloromethane and *n*-hexane were purchased from Mallinckrodt Baker (Phillipsburg, USA) and ethanol P.A. was purchased from Quemis (São Paulo, Brazil) and treated on our own laboratory. Water was purified with a Milli-Q system (Millipore, São Paulo, Brazil).

The racemic sulfoxides (1–11) (Fig. 2) were prepared by oxidation of the corresponding sulfide using oxo diperoxo complexes of molybdenum [22]. The necessary sulfides to prepare the sulfoxides (1–7 and 9–11) were synthesized reacting the thiols with sodium hydride, previously suspended in tetrahydrofuran, with methyl iodide. The obtained sulfides were purified by open column chromatography over silica gel (230–400 mesh) using *n*-hexane/ethyl acetate (1:1 *v*/*v*) as eluent. For sulfoxide 8, the sulfide was gently donated by Prof. Dr. Alfredo Ricardo Marques de Oliveira from the Federal University of Parana, Brazil. All sulfoxides were characterized by NMR and infra-red spectroscopy. Modafinil (12) was prepared as previously described [14], albendazole sulfoxide (13), and the proton pump inhibitors (PPIs): omeprazole (14), pantoprazole (15), rabeprazole (16), and lansoprazole (17) were donated by Ouro Fino Saúde Animal (Ribeirão Preto, SP, Brazil), LIBBS (São Paulo, SP, Brazil), Eurofarma (São Paulo, SP, Brazil), Elisai Co. Clinical Research Center (Tokyo, Japan) and Boehringer Ingelheim (São Paulo, SP, Brazil), respectively.

The chiral columns (250 × 4.6 mm I.D., 5 μm particle size, 200 Å pore size) P-CAP and P-CAP DP were commercially available from Advanced Separations Technologies (Whippany, NJ, USA) and DEAVB is a commercial prototype column.

Calculations

The dead time (t_0) was estimated using the peak resulting from the change in refractive index from the injection of solvent. The retention factor (k) was calculated using the equation $k = (t_r - t_0)/t_0$. The separation factor (α) was calculated using $\alpha = k_2/k_1$. The resolution factor (R_s) was calculated using the equation $R_s = 1.8\ (t_2 - t_1)/(w_2 + w_1)$, where k_2 and k_1 are the retention times of the second and first enantiomers, respectively, and w_1 and w_2 are the corresponding peak widths measured on half height.

Equipment

The LC system consisted of a Shimadzu LC-10AD pump (Kyoto, Japan), an SPD-10A variable wavelength UV–Vis detector, an SIL-10A auto injector with a 500 μL loop and a CD-2095*plus* from JASCO. This equipment is connected to a CBM-10A and for data acquisition Labsolutions software from Shimadzu was used.

Column Evaluations

A series of sulfoxide compounds (Fig. 2) was evaluated on the P-CAP, PCAP–DP and DEAVB columns in the normal phase mode using *n*-hexane/ethanol, *n*-hexane/2-propanol, dichloromethane/methanol, *n*-hexane/methyl *t*-butyl ether/2-propanol and *n*-hexane/methyl *t*-butyl ether/ethanol as mobile phases. The evaluations in the polar organic mode were carried out using ethanol, methanol, acetonitrile and in the reversed-based

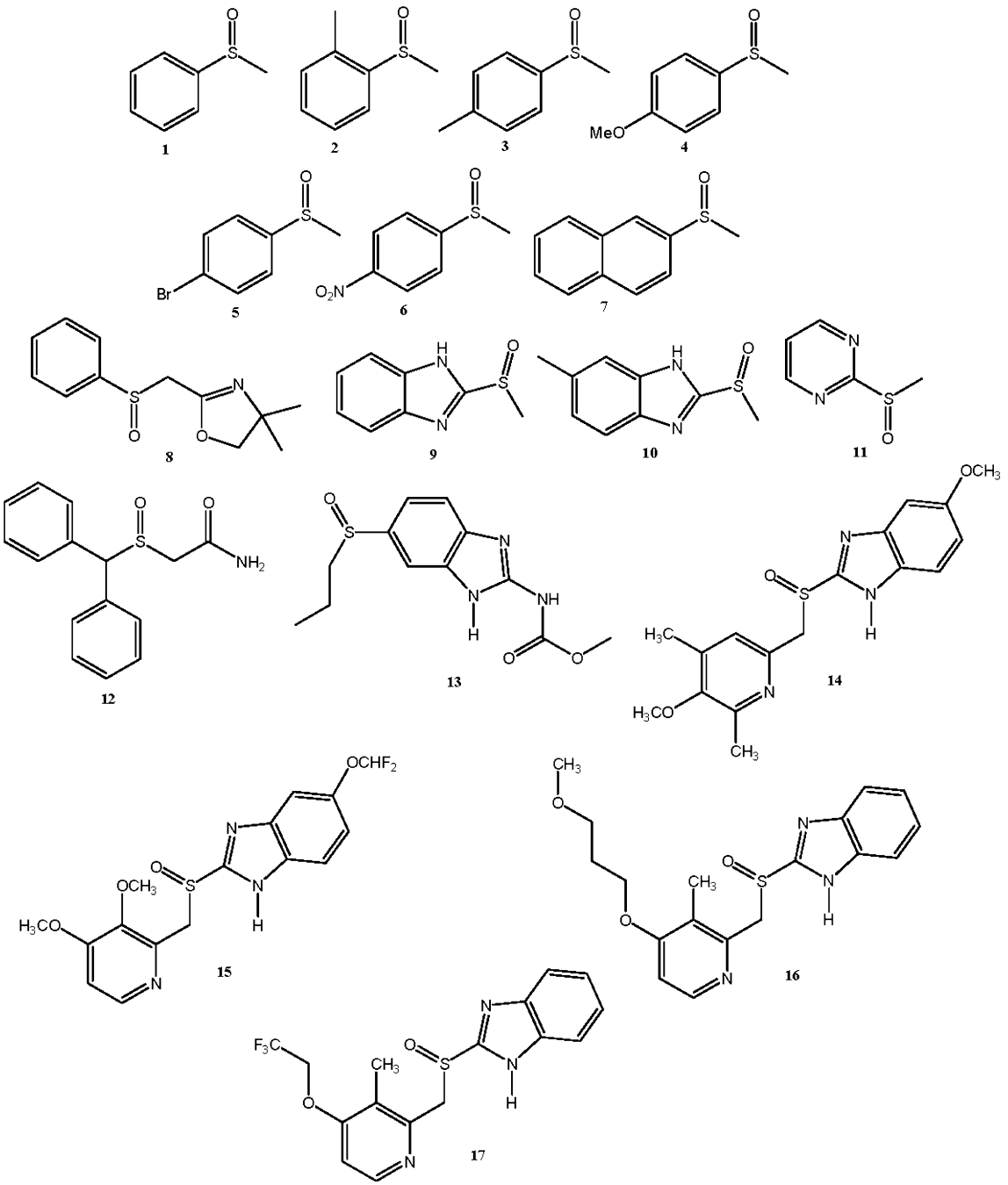


Fig. 2. Chemical structures of chiral sulfoxides series evaluated

mode using methanol/water and ethanol/water as the mobile phases.

The *n*-hexane/ethanol was evaluated systematically, from 100 to 10% (by volume) of ethanol in increments of 10% each time. To compare the influence of the modifier, *n*-hexane/2-propanol was evaluated at compositions that produced comparable retention factors for the best separations achieved with *n*-hexane/ethanol.

The dichloromethane/methanol was evaluated in the compositions (99:01) and (95:05). The *n*-hexane/methyl *t*-butyl ether/2-propanol mobile phase was evaluated in the compositions of (50:25:25) and (40:35:25) while *n*-hexane/methyl *t*-butyl ether/ethanol at (30:45:25) composition.

Acetonitrile/methanol was evaluated systematically, from 100 to 0% of methanol with 10% incremental changes. The methanol/water was evaluated in the range of 90–70% of methanol with

Table 1. Optimized chromatographic data for the enantioseparations of chiral sulfoxides on the P-CAP column and on the P-CAP DP

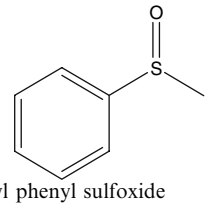
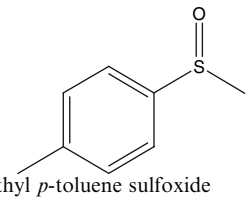
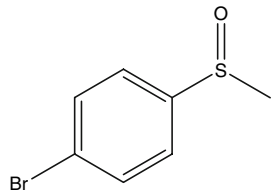
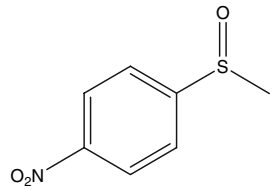
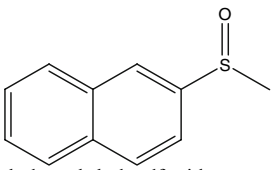
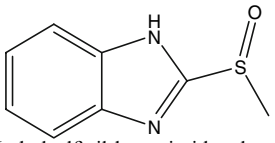
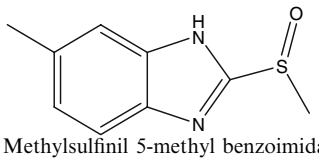
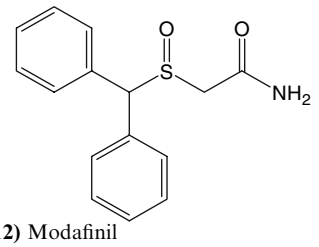
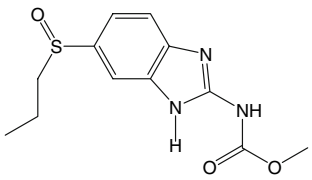
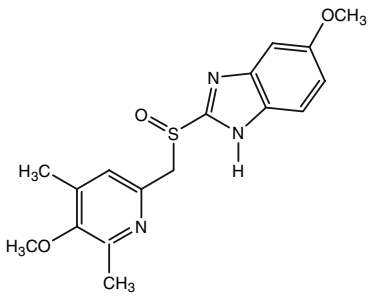
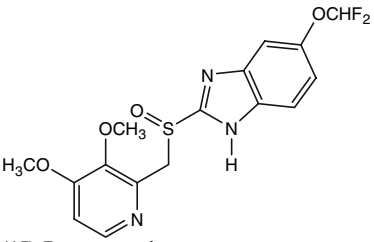
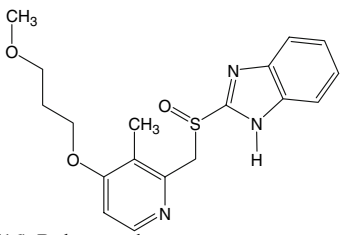
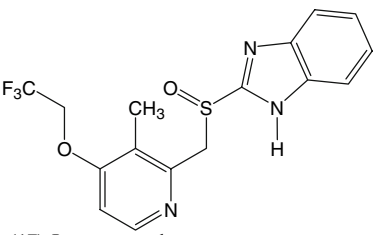
Structure	Mobile phase *v*/*v*	Column	k_1	α	R_s
 **(1)** Methyl phenyl sulfoxide	*n*-Hexane/EtOH (90:10)	P-CAP DP	3.56	1.33	0.86
	ACN (100%)	P-CAP DP	1.06	1.07	0.73
 **(3)** Methyl *p*-toluene sulfoxide	*n*-Hexane/EtOH (90:10)	P-CAP DP	2.87	1.03	0.68
	ACN (100%)	P-CAP DP	1.77	1.05	0.68
 **(5)** 4-(Bromophenyl) methyl sulfoxide	*n*-Hexane/EtOH	P-CAP	1.68	1.04	0.68
	(90:10)	P-CAP DP	3.29	1.04	0.83
	ACN (100%)	P-CAP DP	1.39	1.06	0.68
 **(6)** 4-(Nitrophenyl) methyl sulfoxide	*n*-Hexane/EtOH	P-CAP	3.80	1.03	0.68
	(90:10)	P-CAP DP	9.05	1.03	0.73
 **(7)** Methyl naphthyl sulfoxide	*n*-Hexane/EtOH	P-CAP	1.85	1.05	0.68
	(90:10)	P-CAP DP	3.92	1.17	1.22
	ACN (100%)	P-CAP	0.99	1.09	0.80
 **(09)** Methylsulfinil benzoimidazole		P-CAP DP	1.70	1.29	1.27
	n-Hexane/EtOH (90:10)	P-CAP	2.98	1.05	0.68
 **(10)** Methylsulfinil 5-methyl benzoimidazole	*n*-Hexane/EtOH (90:10)	P-CAP	2.38	1.05	0.68

Table 1. continued

Structure	Mobile phase *v*/*v*	Column	k_1	α	R_s
 **(12)** Modafinil	*n*-Hexane/EtOH (90:10)	P-CAP	13.3	1.05	0.73
		P-CAP DP	11.0	1.08	1.07
	CH_2Cl_2/MeOH (99:01)	P-CAP	2.47	1.11	1.00
	ACN (100%)	P-CAP	3.68	1.10	0.90
 **(13)** Albendazole sulfoxide	*n*-Hexane/EtOH (90:10)	P-CAP	5.75	1.07	0.73
	ACN (100%)	P-CAP	11.3	1.19	0.90
 **(14)** Omeprazole	*n*-Hexane/EtOH (90:10)	P-CAP	8.89	1.13	1.15
		P-CAP DP	9.42	1.08	0.78
	ACN (100%)	P-CAP	6.23	1.05	0.80
 **(15)** Pantoprazole	*n*-Hexane/EtOH (90:10)	P-CAP	9.21	1.09	0.90
	CH_2Cl_2/MeOH (99:01)	P-CAP	2.60	1.10	0.68
	ACN (100%)	P-CAP	5.32	1.16	0.90
 **(16)** Rabeprazole	ACN (100%)	P-CAP	5.87	1.10	0.73
 **(17)** Lansoprazole	*n*-Hexane/EtOH (90:10)	P-CAP DP	13.6	1.06	0.68
	ACN (100%)	P-CAP	4.64	1.07	0.80

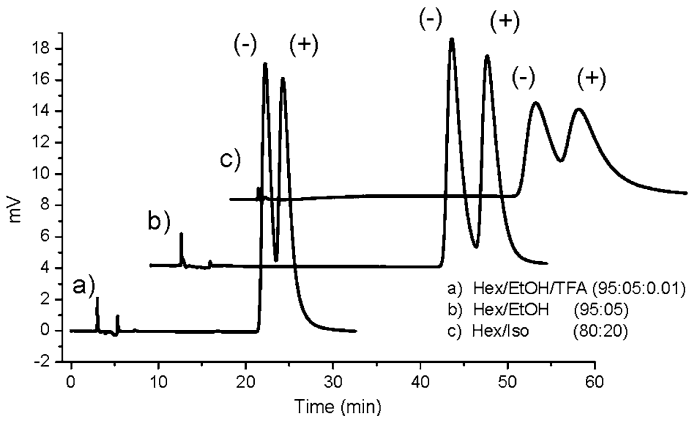


Fig. 3. Chromatograms for omeprazole ($\lambda = 302$ nm) on P-CAP

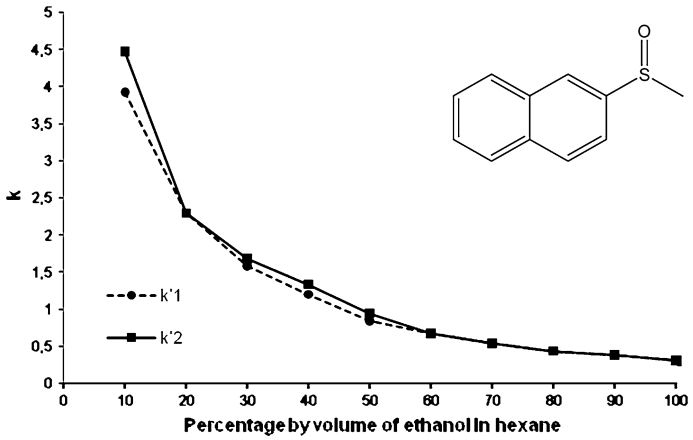


Fig. 4. Methyl naphthyl sulfoxide retention profile on P-CAP DP on normal mode

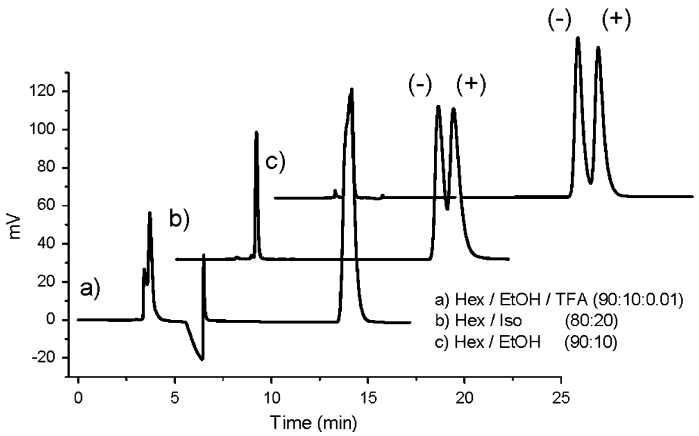


Fig. 5. Chromatograms of methyl naphthyl sulfoxide ($\lambda = 254$ nm) on P-CAP DP

changes also of 10%. The ethanol/water was evaluated at the composition of (70:30).

The mobile phase compositions are always given as volume percents. The flow rate of the analyses was 1 mL min^{-1}, except for the evaluation using ethanol/water which was 0.5 mL min^{-1}. Finally, when using a new mobile phase, 10 column volumes of solvent were pumped through prior to the injection of the analytes.

Results and Discussion

Performance of P-CAP and P-CAP DP

A total of 11 racemic sulfoxides (65%) were separated in the three elution modes with the P-CAP column, while with the P-CAP DP column eight (43%) separations were obtained. In the normal phase mode (i.e., *n*-hexane/ethanol as the mobile phase) nine chiral sulfoxides (53%) were separated on the P-CAP and eight (47%) on the P-CAP DP. Sulfoxides 5, 6, 9, 10 and sulfoxides 6, 12, 14, 17 were separated on the P-CAP and P-CAP DP columns, respectively. In both cases, only in this specific elution mode (Table 1).

The retention behavior for all compounds on the P-CAP CSP was typical of the normal elution mode. Separations were achieved when the composition of the mobile phase had lower percentages of ethanol. The omeprazole enantiomers, for example, were better separated, with a high retention factor, when *n*-hexane/ethanol (95:05 *v*/*v*) was used as mobile phase (Fig. 3).

Although this profile was also observed on the P-CAP DP column for this series of sulfoxides, several exhibited somewhat unusual chiral discrimination trends. For example, methyl naphthyl sulfoxide (7) had separation factors of 1.17 and 1.12, when *n*-hexane/ethanol (90:10) and (60:40) were used respectively, as mobile phases. Yet no separation was observed with *n*-hexane/ethanol (80:20) (Fig. 4).

2-propanol also was evaluated as a modifier in the normal elution mode; however, the enantioresolution for all compounds on both columns, decreased when compared to the use of ethanol. Figures 3 and 5 are typical examples showing that ethanol is a better modifier in the normal phase mode for the P-CAP and P-CAP DP columns, at least for the series of compounds evaluated.

It has been reported that the use of additives such as trifluoroacetic acid (TFA) diminishes the retention time, decreases tailing and produced sharper

peaks of some chiral compounds on the P-CAP [14] and P-CAP DP columns [15]. The use of TFA as mobile phase additive also decreased the retention times of the sulfoxides analyzed (Figs. 3, 5). However, its use provided lower interaction between analytes and stationary phase, worsening their enantioseparations. As an example, omeprazole had separation factor ($\alpha = 1.13$) and resolution ($R_s = 1.38$) using *n*-hexane/ethanol (95:05) that changed to $\alpha = 1.10$, $R_s = 0.96$ with *n*-hexane/ethanol/TFA (95:05:0.01) on P-CAP (Fig. 3) and methyl naphthyl sulfoxide had $\alpha = 1.16$, $R_s = 1.22$ using *n*-hexane/ethanol (90:10) whereas no separation was observed with *n*-hexane/ethanol/TFA (90:10:0.01) on P-CAP DP (Fig. 5).

The polar organic mode was used to separate seven of the chiral sulfoxides on the P-CAP columns (41%) and four on the P-CAP DP (24%). On the latter column, the polar organic mode proved to be complementary to the normal mode in that it separated two new sulfoxides (16 and 17) that were not otherwise resolved.

Relatively poor enantiomeric separations were obtained when using the polar organic mode on the P-CAP DP column. Moreover, the four chiral sulfoxides separated in this elution mode, were also separated in the normal mode. For both columns, acetonitrile was a better modifier than methanol, in the polar organic mode, as it provided all the separations obtained. In fact, all compounds were separated only when a 100% acetonitrile mobile phase was used.

Finally, the use of the normal-phase mode with CH_2Cl_2/MeOH (99:01) as the mobile phase separated just two chiral sulfoxides (11%) (12 and 15) on the P-CAP column; however, it was responsible for a small increase in the separation of modafinil enantiomers, (see Table 1). In addition, no separations were obtained with CH_2Cl_2/MeOH (99:01) on the P-CAP DP column.

Performance of the DEAVB CSP

The highest success rate for the resolution of this chiral sulfoxide series was with the DEAVB column in the normal phase mode. 13 sulfoxides (76%) were separated, five of them with baseline resolution.

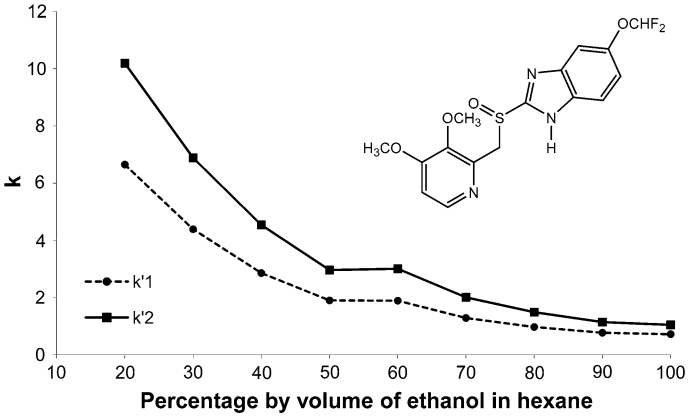


Fig. 6. Pantoprazole retention profile on DEAVB on normal mode

The DEAVB column showed exceptionally high enantiorecognition capabilities especially for compounds (12, 14, 15, 16 and 17). Retention factors profiles were typical of the normal phase elution mode. It should be noted that larger resolutions were obtained with higher amounts of *n*-hexane in the mobile phase. However, good separation factors and R_s were also obtained with low percentage of *n*-hexane. For example, $\alpha = 1.48$ and $R = 2.28$ were attained for pantoprazole using a mobile phase of (10:90) *n*-hexane/ethanol (Fig. 6).

The use of 2-propanol, as modifier, or TFA, as a mobile phase additive, produced somewhat inferior separations with the DEAVB column, just as it did for the P-CAP and P-CAP DP columns.

With polar organic mobile phases, seven racemic sulfoxides were separated (41%), four of them baseline (Table 2). Although, methanol also was effective for the separation of compounds (9, 10, 12, 14, 15 and 17), with enantioresolutions ranging from 0.68 to 1.57, the use of acetonitrile always provided better results (Table 2). The use of 10% of methanol in acetonitrile gave slightly better resolutions than with the use of 100% of methanol, except for omeprazole (14) in which the R_s decreased from 1.57 to 1.25. All other polar organic mobile phase compositions examined decreased the enantioresolutions obtained by the use of neat acetonitrile or neat methanol.

The use of CH_2Cl_2/MeOH (99:01) produced highly effective separations with the DEAVB column. Although, only five chiral sulfoxides (12, 14, 15, 16, 17) of the series were separated (29%), the R_s range was from 2.18 to 4.13. Resolutions in the range of 2.07–3.41 (Table 2) were obtained for these sulfoxides drugs with the use of another non standard mobile phase, *n*-hexane/MtBE/EtOH (30:45:25) (Table 2). For the PPIs 14, 16 and 17, the resolutions obtained with this mobile phase represented a major increase in resolution, while for modafinil (12) the resolution, when compared with CH_2Cl_2/MeOH (99:01), dropped over 50%. The use of 2-propanol in place of ethanol provided high retentions factors and was not pursued further.

Although, it was known that the main requirement for chiral selectivity of these evaluated polymeric columns is hydrogen bonding and that this interaction is enhanced on organic solvents [15, 18, 19], the reversed phase mode was evaluated for the sulfoxide series in these three columns. The P-CAP P-CAP DP columns were not able to resolve any of the selected sulfoxides in the reversed phase mode. However, due to an improved selectivity caused by an extended π system, higher rigidity and steric hindrance [19] the use of the DEAVB column in the reversed phase mode with methanol as modifier, also proved to be effective for the separation of the enantiomers of the proton pump inhibitors (PPIs) (14–17). These racemic sulfoxide-drugs were baseline separated

Table 2. Optimized chromatographic data for the enantioseparations of chiral sulfoxides on the DEAVB column

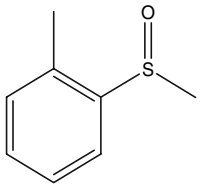
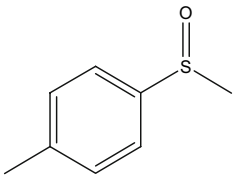
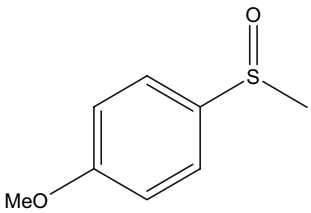
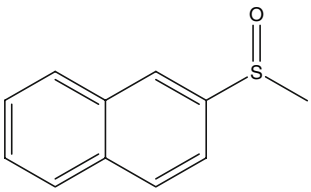
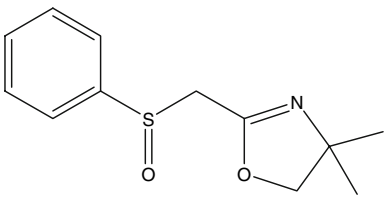
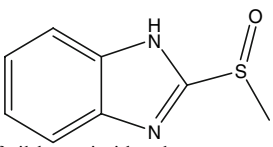
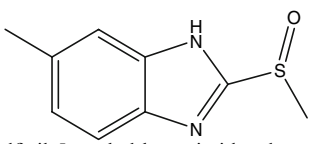
Structure	Mobile phase *v*/*v*	k_1	α	R_s
 **(2)** Methyl *o*-toluene sulfoxide	*n*-Hexane/EtOH (90:10)	1.36	1.50	0.78
 **(3)** Methyl *p*-toluene sulfoxide	*n*-Hexane/EtOH (90:10)	1.36	1.03	0.68
 **(4)** 4-(Methoxyphenyl) methyl sulfoxide	*n*-Hexane/EtOH (90:10)	2.84	1.05	1.04
 **(7)** Methyl naphthyl sulfoxide	*n*-Hexane/EtOH (80:20)	1.77	1.03	0.68
 **(08)** 2-Benzenesulfenilmethyl-4,4-dimethyl-4,5-dihidrooxazole	*n*-Hexane/EtOH (80:20)	1.40	1.04	0.68
 **(09)** Methylsulfinil benzoimidazole	*n*-Hexane/EtOH (80:20)	2.98	1.05	0.91
 **(10)** Methylsulfinil 5-methyl benzoimidazole	ACN (100%) *n*-Hexane/EtOH (80:20)	0.43 1.38	1.15 1.07	0.78 0.78

Table 2. continued

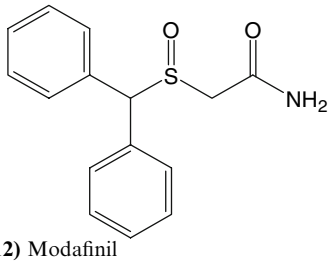
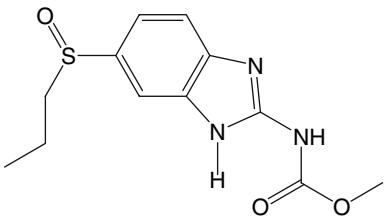
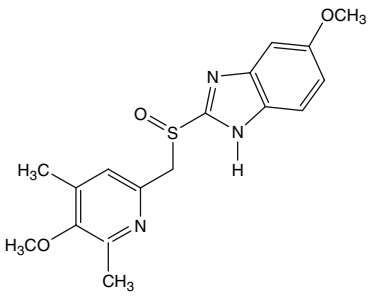
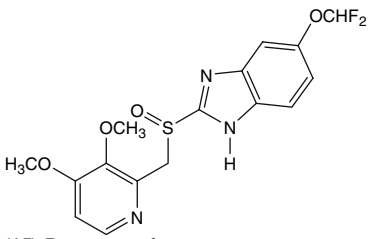
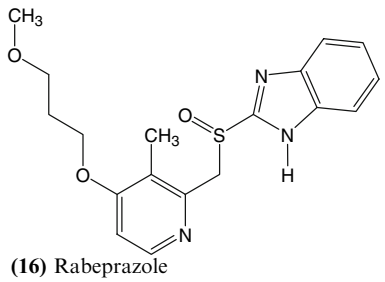
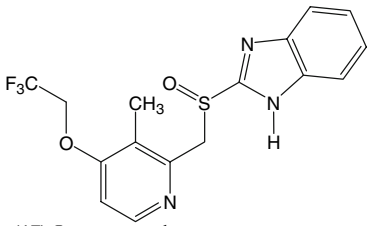
Structure	Mobile phase *v*/*v*	k_1	α	R_s
 **(12)** Modafinil	ACN (100%)	0.45	1.15	0.73
	n-Hexane/EtOH (80:20)	5.12	1.21	4.76
	CH_2Cl_2/MeOH (99:01)	3.33	1.41	3.31
	n-Hexane/MtBE/EtOH (30:45:25)	4.16	1.21	3.65
	ACN (100%)	0.92	1.23	0.91
 **(13)** Albendazole sulfoxide	*n*-Hexane/EtOH (80:20)	2.82	1.03	0.68
 **(14)** Omeprazole	*n*-Hexane/EtOH (80:20)	4.76	1.55	4.68
	CH_2Cl_2/MeOH (99:01)	3.31	1.37	2.75
	n-Hexane/MtBE/EtOH (30:45:25)	3.65	1.57	3.41
	ACN (100%)	1.913	1.37	2.16
	MeOH/H_2O (70:30)	3.42	1.30	2.18
	EtOH/H_2O (70:30)	2.08	1.32	2.45
 **(15)** Pantoprazole	*n*-Hexane/EtOH (80:20)	6.55	1.56	5.15
	CH_2Cl_2/MeOH (99:01)	3.56	1.50	3.67
	n-Hexane/MtBE/EtOH (30:45:25)	3.23	1.59	3.58
	ACN (100%)	1.01	1.40	2.37
	MeOH/H_2O (70:30)	2.82	1.30	2.20
	EtOH/H_2O (70:30)	1.33	1.42	2.55
 **(16)** Rabeprazole	*n*-Hexane/EtOH (80:20)	4.62	1.47	4.29
	CH_2Cl_2/MeOH (99:01)	3.29	1.33	2.18
	n-Hexane/MtBE/EtOH (30:45:25)	3.13	1.49	3.24
	ACN (100%)	1.68	1.27	1.59
	MeOH/H_2O (70:30)	1.70	1.30	1.70
	EtOH/H_2O (70:30)	2.00	1.29	2.27

Table 2. continued

Structure	Mobile phase *v*/*v*	k_1	α	R_s
 **(17)** Lansoprazole	*n*-Hexane/EtOH (80:20)	2.96	1.35	3.49
	CH_2Cl_2/MeOH (99:01)	2.96	1.20	1.60
	n-Hexane/MtBE/EtOH (30:45:25)	1.59	1.34	2.34
	ACN (100%)	0.84	1.23	1.26
	MeOH/H_2O (70:30)	2.23	1.20	1.60
	EtOH/H_2O (70:30)	1.60	1.22	1.68

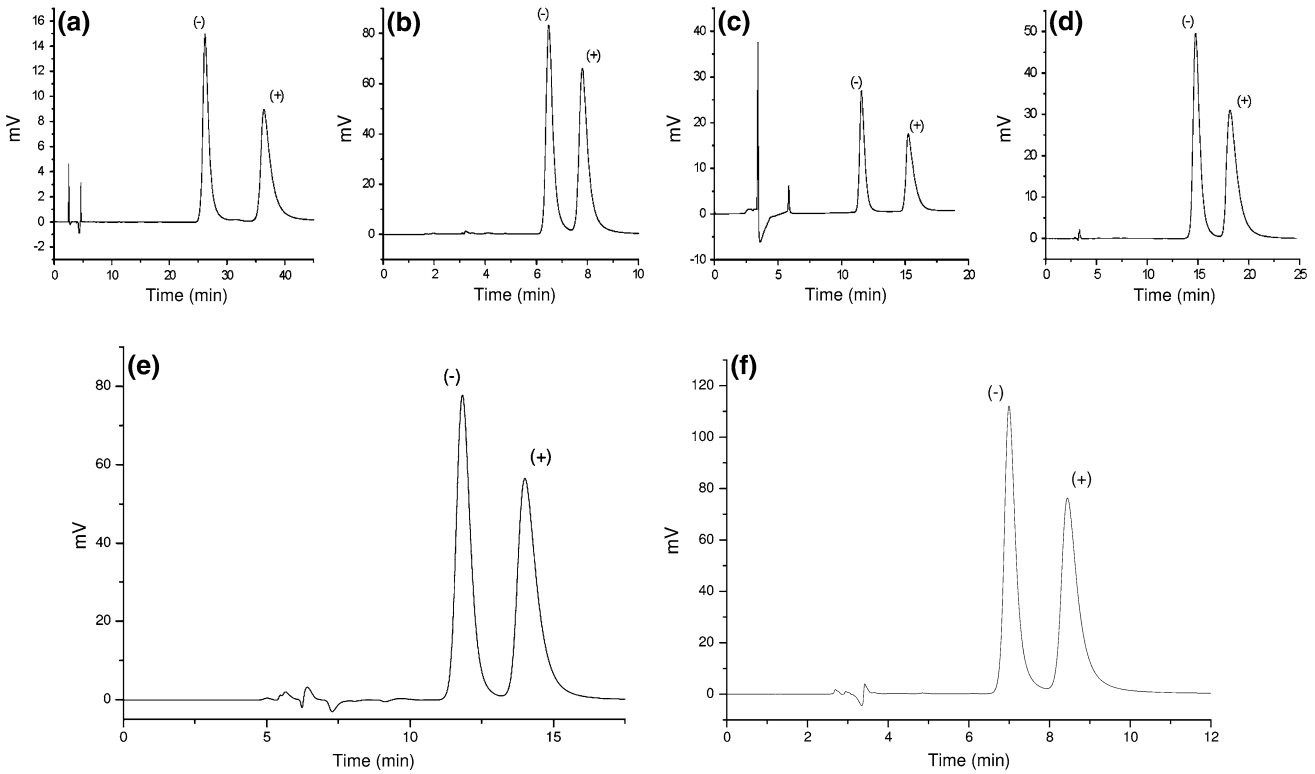


Fig. 7. Chromatograms of, (**a**) rabeprazole, $\lambda = 285$ nm *n*-hexane/EtOH (80:20 *v*/*v*). (**b**) pantoprazole, $\lambda = 285$ nm ACN (100%), (**c**) modafinil $\lambda = 240$ nm CH_2Cl_2/MeOH (99:01 *v*/*v*), (**d**) omeprazole, $\lambda = 302$ nm MeOH/H_2O (70:30 *v*/*v*), (**e**) pantoprazole, ETOH/H_2O (70:30 *v*/*v*), (**f**) lansoprazol, $\lambda = 285$ nm *n*-hexane/MtBE/ETOH (30:45:25 *v*/*v*) on DEAVB

with methanol/water (70:30) (Table 2). This is the first report of the use of these chiral polymeric columns in the reversed phase mode and it is a particular interesting result since acetonitrile is normally the modifier used for enantioresolution of these PPIs in this elution mode on all polysaccharide-based CSPs [21, 23–26].

In trying to achieve resolution of these drugs in the reversed-based mode using a friendlier environmental mobile phase, the use of ethanol was examined. PPIs (14–17) were separated with resolutions from 1.68 to 2.55 with shorter retentions times using ethanol as modifier (Table 2).

The chromatograms in Fig. 7 show the separations obtained using the DEAVB column with different modes of elution. The normal phase elution mode was the most effective approach allowing the highest resolutions, except for the drug modafinil (12) that had the highest resolution ($R_s = 4.13$) when CH_2Cl_2/MeOH (99:01) was used. However, lower retention factors were obtained by the use of a 100% of ACN mobile phase indicating that this might be preferable for strictly analytical separations.

Comparison of the P-CAP, P-CAP DP and DEAVB Columns

The three polymeric CSPs columns evaluated showed chiral discrimination for a series of 17 chiral sulfoxides. Only sulfoxide (11) was not separated with

any of the mobile phases examined. Methyl naphthyl sulfoxide (7) had the highest R_s when the P-CAP DP column was used, although this was the column with lower chiral discrimination power for the other chiral sulfoxides. Sulfoxides (5, 6, 9 and 10), with low steric volumes (Fig. 2) were more poorly separated on the P-CAP column in the normal and polar organic elution modes.

The DEAVB column was the most effective of the three chiral polymer columns used and was able to separate 13 out of 17 racemic sulfoxides. Furthermore it was able to baseline separate the drug modafinil (12), using different organic mobile phases while the benzoimidazoles sulfoxides-drugs (14–17) were enantioseparated in all organic and aqueous conditions evaluated with high resolutions (see Table 2). The resolutions achieved for these sulfoxide drugs infer that this is not only a result of CSP–sulfoxides interactions, but it is, also, a function of steric fit. The sulfoxides with a large substituent near the stereogenic center are most effectively separated by this column. The graphics of Fig. 8 summarizes the enantioseparations achieved in all elution modes.

The three synthetic polymeric columns have complementary selectivities for the series of racemic sulfoxides examined. Four of the series (1, 2, 4 and 8) were separated on just one column. Figure 9 shows which compounds were separated by more than one column.

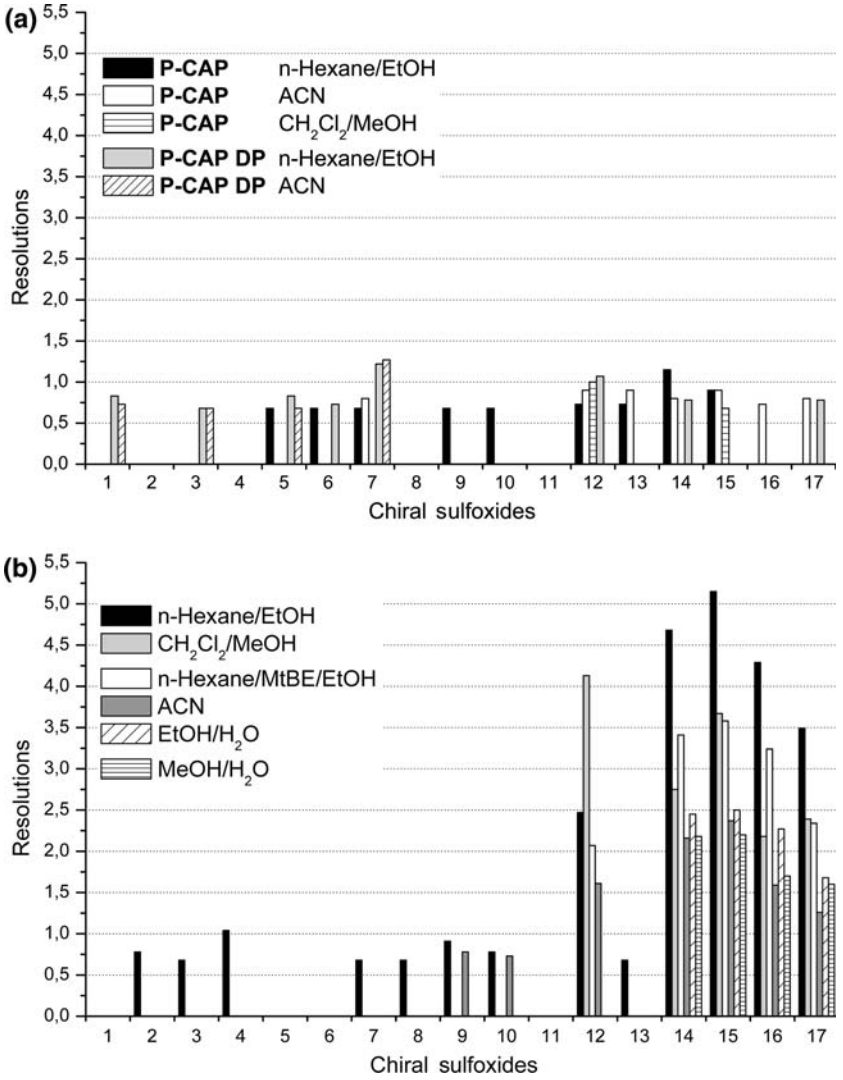


Fig. 8. Graphics illustrating the enantioresolutions of the chiral sulfoxides series on (**a**) P-CAP, P-CAP DP, (**b**) DEAVB using a diversity of mobile phase modes

Conclusions

This work expands the applicability of a new series of polymeric columns for the enantioresolution of a wide range of chiral sulfoxides. A diversity of mobile phases, including non standard ones, can be explored to boost the selectivity and enhance the use of these CSPs. The relatively greater effectiveness of the DEAVB column in different elution modes, including the reversed phase mode, enables this CSP to be exploited for both quantitative drug analysis and preparative separations.

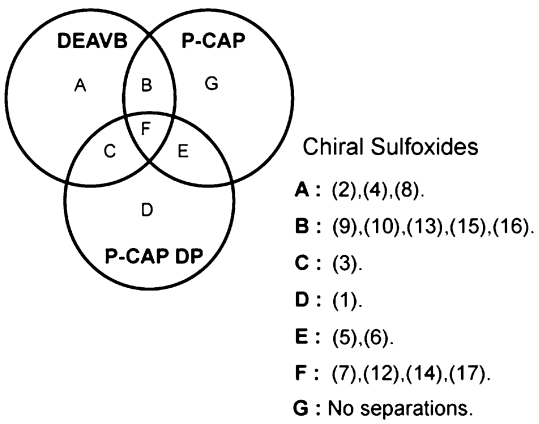


Fig. 9. Graphic illustrating the complementarities in resolution of the columns P-CAP, P-CAP DP and DEAVB

Acknowledgments

This study was supported by the Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP). The authors also acknowledge the Conselho Nacional de Desenvolvimento Científico e Técnologico (CNPq) and the manufactures for the donations of several chiral sulfoxides. We gratefully acknowledge the support from the National Institute of Health (GM053825-11 and GM053825-12) for this work.

References

1. Lin G, Li Y, Chan ASC (2001) Introduction. In: Principles and applications of asymmetric synthesis. Wiley, New York, pp 7–8
2. Rayner DR, Gordon AJ, Mislow K (1968) J Am Chem Soc 90:4854–4860
3. Fernandez I, Khiar N (2003) Chem Rev 103:3651–3705
4. Harrison PWB, Kenyon J, Phillips H (1926) J Chem Soc pp 2079–2090
5. Kuesters E, Gerber G (1997) Chromatographia 44:91–96
6. Anderson JL, Ding J, McCulla RD, Jenks WS, Armstrong DW (2002) J Chromatogr A 946:197–208
7. Balmer K, Persson B-A, Lagerstroem P-O (1994) J Chromatogr A 660:269–273
8. Berthod A, Xiao TL, Liu Y, Jenks WS, Armstrong DW (2002) J Chromatogr A 955:53–69
9. Matlin SA, Tiritan ME, Cass QB, Boyd DR (1996) Chirality 8:147–152
10. Chankvetadze B, Yamamoto C, Okamoto Y (2001) J Chromatogr A 922:127–137
11. Cass QB, Batigalhia F (2003) J Chromatogr A 987:445–452
12. Belaz KRA, Coimbra M, Barreiro JC, Montanari CA, Cass QB (2008) J Pharm Biomed Anal 47:81–87
13. Belaz KRA, Cass QB, Oliveira RV (2008) Talanta 76:146–153
14. Cass QB, Ferreira Galatti T (2008) J Pharm Biomed Anal 46:937–944
15. Zhong Q, Han X, He L, Beesley TE, Trahanovsky WS, Armstrong DW (2005) J Chromatogr A 1066:55–70
16. Gasparrini F, Misiti D, Villani C (2003) WO 2003079002, p 25
17. Gasparrini F, Misiti D, Villani C, Rompietti R (2003) In: Abstracts of the 15th international symposium on chirality (ISCD-15), Shizuoka, Japan, p 132
18. Han X, He L, Zhong Q, Beesley TE, Armstrong DW (2006) Chromatographia 63:13–23
19. Han X, Wang C, He L, Beesley TE, Armstrong DW (2007) Anal Bioanal Chem 387:2681–2697
20. Montanari MLC, Cass QB, Andricopulo AD, Leitao A, Montanari CA (2005) Anal Chim Acta 545:33–45
21. Montanari MLC, Cass QB, Leitao A, Andricopulo AD, Montanari CA (2006) J Chromatogr A 1121:64–75
22. Batigalhia F, Zaldini-Hernandes M, Ferreira AG, Malvestiti I, Cass QB (2001) Tetrahedron 57:9669–9676
23. Bonato PS, Paias FO (2004) J Braz Chem Soc 15:318–323
24. Cirilli R, Ferretti R, Gallinella B, De Santis E, Zanitti L, La Torre F (2008) J Chromatogr A 1177:105–113
25. Cass QB, Degani ALG, Cassiano NM, Pedrazolli J (2002) J Chromatogr B 766:153–160
26. Cass QB, Lima VV, Oliveira RV, Cassiano NM, Degani ALG, Pedrazzoli J (2003) J Chromatogr B 798:275–281